Effects of pacing-induced ischemia on early left ventricular filling and regional myocardial dynamics and their modification by nifedipine

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ABSTRACT The effect of pacing-induced ischemia on early left ventricular filling and regional myocardial lengthening was studied in 11 patients with coronary artery disease (CAD) and six control patients with normal coronary arteriograms. All of the 11 patients with CAD developed typical anginal pain during pacing tachycardia, and in the postpacing beat, the left ventricular end-diastolic pressure (LVEDP) rose from 13 ± 4 to 26 ± 4 mm Hg (mean ± SD, p < .01), the relaxation time constant increased from 43 ± 9 to 59 ± 7 msec (p < .01), and the ejection fraction diminished from 62.1 ± 6.7 to 51.6 ± 10.6% (p < .01). However, the peak rate of early left ventricular filling (LVPF) obtained from frame-by-frame analysis of left ventriculograms and the LVFP normalized for the stroke volume and for the end-diastolic volume did not change significantly. In the ischemic segment, the peak rate of lengthening (PL) decreased by 45% with ischemia, and the PL normalized for the end-diastolic segment length decreased by 42%. However, the PL normalized for the extent of systolic shortening did not change. In the control segment there was a tendency for these three variables to increase, but the changes were not statistically significant. The time difference from the PL to the LVFP increased significantly in the ischemic segment (31 ± 28 vs 75 ± 48 msec, p < .05). Although the LVEDP rose slightly but significantly from 9 ± 3 to 12 ± 5 mm Hg (p < .05) in the control patients in the postpacing beat, the other global hemodynamic variables and the variables of regional myocardial dynamics did not change. The administration of nifedipine in six patients with CAD resulted in the disappearance or diminution of anginal pain even with the same duration and rate of pacing and was associated with restoration of global systolic function and regional myocardial shortening and lengthening in the ischemic segment. In the control segment, the three variables of segmental lengthening increased with administration of nifedipine. Thus, the segmental myocardial lengthening rate decreased with ischemia due to a decrease in segmental shortening and impairment of myocardial distensibility. The LVFP did not decrease with ischemia despite impairment in isovolumetric relaxation, accentuation of asynchrony in left ventricular filling, and a decrease in the PL in the ischemic segment because of an increase in the PL in the nonischemic segment secondary to an increase in left ventricular filling pressure. Administration of nifedipine resulted in improvement in segmental lengthening in the ischemic as well as in the control segment in the postpacing beat. Circulation 76, No. 6, 1232–1244, 1987.

PREDOMINANT left ventricular filling occurs during so-called rapid ventricular filling in the early phase of diastole. Effective early ventricular filling is important for ventricular ejection, and the rate of early ventricular filling is thought to be influenced by left ventricular performance, relaxation, and the pressure gradient between the left atrium and the left ventricle during this period. Therefore, factors that can alter ventricular ejection, relaxation, and left atrial pressure may have an indirect as well as a direct effect on early ventricular filling.

Myocardial ischemia has been known to depress ventricular systolic function and relaxation; however, its effect on early ventricular filling is controversial. Most previous studies have paid attention to overall ventricular filling. Since an ischemic insult is mostly regional in nature, the analysis of
regional myocardial function in addition to the determination of global ventricular performance is crucial.\textsuperscript{10-12} Furthermore, many previous studies have not focused on the interaction between ventricular filling and ejection or relaxation.

The present study was designed to investigate regional myocardial dynamics in addition to global ventricular filling in patients with coronary artery disease (CAD) during postpacing ischemic periods. In some of the patients studied, we tested the effects of a calcium-channel blocker, nifedipine, on regional and global ventricular function with special attention to early ventricular filling during ischemia. The results for early ventricular filling were analyzed in relation to ventricular systolic function and relaxation.

**Methods**

**Study patients.** Our 17 patients (seven women and 10 men) were 21 to 72 years old. Eleven of the 17 patients had effort-induced angina pectoris (patients with CAD), and two of the 11 patients with CAD had had a prior myocardial infarction, but patients with unstable angina or acute myocardial infarction were excluded. Six patients with chest pain but normal coronary arteriograms and left ventriculograms served as controls. All patients were in sinus rhythm.

**Catheterization and cineangiography.** All patients gave informed consent. Premedication consisted of 5 mg of diazepam orally 1 hr before cardiac catheterization. All medications were withheld for at least 12 hr before the procedure. Catheterization was performed via the brachial approach. After routine right heart catheterization with a Swan-Ganz catheter and left heart catheterization with a Sones catheter, coronary arteriography was performed by the Sones technique. A pacing catheter was then positioned in the right atrium. A high-fidelity micromanometer-tipped angiocatheter (Mikro-tip, model PC-481, Millar Instruments) was introduced into the left ventricle of 12 patients. In five patients, a No. 8F NIH catheter was used for left ventriculography. When a micromanometer-tipped catheter was used, the baseline drift was checked by comparison with a Statham P23Db transducer connected to the catheter’s fluid-filled lumen for angiography. The zero level of the fluid system was set at the midchest position. When it was confirmed that ventricular pressure had returned to the baseline after coronary arteriography, left ventricular cineangiography was performed in the 30° right anterior oblique projection with a Phillips 9 inch image intensification system. Left ventricular opacification was achieved by injecting 25 to 35 ml of radiopaque contrast medium (80% Angiograin) through the catheter at a rate of 12 ml/sec. Films were exposed at a rate of 60 frames/sec with an Art 35 mm cine camera. When a micromanometer-tipped catheter was used, high-fidelity left ventricular pressure, the electrocardiogram, cineangiographic frame markers, and an injection marker were simultaneously recorded at a paper speed of 100 mm/sec with a multichannel optical recording system (VR-12 Simultrace Recorder, Electronics for Medicine). Two lead markers were placed on the image intensifier as fixed external references for the superimposition of the images.

**Pacing protocol.** Atrial pacing was initiated at a rate of 90 beats/min and was increased in increments of 30 beats/min every 2 min. In patients in whom atrioventricular block developed during atrial pacing, right ventricular pacing was substituted. Pacing was stopped with the occurrence of chest pain. If well tolerated, pacing was continued at a rate of 150 beats/min for 6 min. Therefore, the maximum total duration of pacing was 10 min (i.e., 90 beats/min for 2 min, 120 beats/min for 2 min, and 150 beats/min for 6 min). The duration of pacing in each patient is summarized in table 1. The second angiogram was obtained immediately after discontinuation of pacing. One beat between the fifth and twelfth beats after discontinuation of pacing was used for pressure and left ventricular volume analyses. Extrasystolic and postextrasystolic beats were excluded.

In six of the 11 patients with CAD, after left ventricular pressure returned to the baseline, 10 mg of nifedipine was administered sublingually. Ten minutes later baseline pressure recordings were made, and pacing was repeated at the same rate and duration as before nifedipine. The third angiogram was obtained in these six patients with CAD in the same manner as the second angiogram. The 1 beat after discontinuation of pacing as close as possible to that same beat on the second angiogram in a given patient was used for the analysis.

**Data analyses.** The method of automatic processing of cineangiograms has been described elsewhere.\textsuperscript{10} Briefly, the left ventricular images on cinefilm were transferred to a computer through a flying spot scanner and were stored on magnetic disk. Each digitized image consisted of 128 × 128 pixels with gray levels of 256 values. A gradient image was then obtained by spatial differentiation of gray levels. The points with the maximal gradient values were traced to delineate the ventricular boundary.

The left ventricular volumes (V) were calculated by a modification of the formula of Kennedy et al.\textsuperscript{13}:

\[
V = 0.687 \times C^3 \times A^{2}/L + 1.9 \text{ ml}
\]

Where A (in cm\(^2\)) is the area of the ventricle calculated from the number of pixels surrounded by the left ventricular boundary, L (in cm) is the longest measured length between the midpoint of the aortic valve and the apex, and C is the linear correction factor for the magnification of a unit of length (1 pixel), which was derived from a comparison with the known area of the filmed 1 cm\(^2\) grid, placed parallel to the tube at the position of the heart.

Sequential ventricular silhouettes were superimposed on the end-diastolic frame throughout the cardiac cycle with the use of two external reference markers. In each superimposed ventricular image, 128 radial grids were drawn from the center of gravity of the end-diastolic silhouette to the endocardial margin and pooled. We have shown previously that with this external reference system, the regional wall motion abnormalities are faithfully represented as predicted by the location of coronary artery lesions.\textsuperscript{10, 14} Ninety of these 128 radii covered the outline of the left ventricular cavity (but not the area of the aortic and mitral valves), which was divided into five sections, with the midpoint at the apex. Accordingly, 18 radial grids were included in each section, which corresponded roughly to the five segments (anterobasal, anterolateral, apical, diaphragmatic, and posterobasal) defined in a reporting system described by the American Heart Association.\textsuperscript{15} Measurement of the length of each grid line throughout the cardiac cycle made it possible to analyze contraction and lengthening of specific segments of the left ventricular myocardium. To analyze the effect of ischemia, and its modification with nifedipine, on the segmental myocardial dynamics, we selected the potentially ischemic segment corresponding to the known coronary lesion in which active shortening was preserved on the control left ventriculogram and compared the response to cardiac pacing with that in the normal section perfused through intact coronary arteries.

End-diastole was defined as the timing of the peak of the R wave on the electrocardiogram. Global end-systole was defined as the time when left ventricular volume became minimum on
the left ventricular volume-time curve, and stroke volume and ejection fraction were calculated in the usual fashion. The extent of shortening was defined here as the difference between the end-diastolic segment length and the minimum segment length obtained from the length of each radial grid plotted against time. Therefore, the timing of the minimum segment length varied in each segment. This definition allows the extent of shortening to become largest and it prevents the value of the peak rate of segmental lengthening normalized for the extent of shortening described below from becoming unfairly large. Percent shortening was defined as extent of shortening × 100/end-diastolic length. The peak rate of left ventricular filling and the peak rate of segmental lengthening were obtained from the left ventricular volume-time curve and the segmental length-time curve with the use of a digital convolution algorithm developed by Savitzky and Golay.16

To determine the contribution to left ventricular filling of left ventricular preload and systolic ejection, we obtained the peak filling rate (LVPF) normalized for the end-diastolic volume (EDV) and the stroke volume (SV) by simple division (LVPF/EDV and LVPF/SV). The peak rate of segmental lengthening (PL) normalized for the end-diastolic segment length (EDL) and the extent of shortening (dL) were also determined (PL/EDL and PL/dL).

The effects of asynchrony on global left ventricular filling were analyzed by determination of the time of the global left ventricular peak filling rate and the segmental peak lengthening rate after mitral opening. The time of mitral valve opening was determined by left ventriculograms and the degree of asynchrony was expressed by the absolute time difference between the time of the global peak left ventricular filling rate and that of the segmental lengthening rate.

Using an electronic digitizer, we measured left ventricular pressure at approximately 5 msec intervals throughout the period of isovolumetric relaxation, defined as the period immediately after maximal negative dP/dt until the time at which pressure had fallen to 5 mm Hg above left ventricular end-diastolic pressure. The coordinates of pressure (P) and time (t) were inserted into the equation: 

\[ P = P_o \exp(-bt + c), \]  

where \( P_o \) is the pressure at maximal negative dP/dt; \( \exp \) is exponential; \( a, b, c \) are constants, by the iterative curve-fitting method with use of the algorithm of the steepest descent.17, 18 The time constant of isovolumetric pressure decay (the relaxation time constant) was determined as 1/b.19

Statistics. All data are expressed as the mean ± SD. The differences between two stages in a given group of patients were tested by the paired t test and the difference between the control patients and those with CAD were tested by the unpaired t test. To examine the statistical significance of the effects of nifedipine, we tested each variable at three different stages in the six patients with CAD by a two-way analysis of variance, and significant differences were located by the Newman-Keuls test. P values less than .05 were considered to indicate a significant difference.

Results

Clinical and angiographic characteristics. All 11 patients with CAD had a significant stenosis (> 75%) in

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/sex</th>
<th>OMI</th>
<th>Coronary anatomy</th>
<th>Baseline LVP/LVEDP (mm Hg)</th>
<th>EDV (ml/m)</th>
<th>EF (%)</th>
<th>Pacing (min)</th>
<th>EDVI (ml/m)</th>
<th>EF (%)</th>
<th>Postpacing EDVI (ml/m)</th>
<th>EF (%)</th>
<th>Nifedipine and postpacing EDVI (ml/m)</th>
<th>EF (%)</th>
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<tr>
<td>1</td>
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<td>LAD</td>
<td>182/19</td>
<td>93</td>
<td>47</td>
<td>10</td>
<td>97</td>
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<td>83</td>
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<td>56</td>
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<td>67</td>
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<td>5</td>
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<td>---</td>
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<td>9</td>
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<td>11</td>
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<td>67</td>
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<td>70</td>
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<td>SD</td>
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<td>11</td>
<td>12</td>
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</table>

EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LAD = left anterior descending artery; LMT = left main trunk; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular peak pressure; OMI = old myocardial infarction; RCA = right coronary artery.
one of the major branches of the coronary artery, and all experienced typical anginal pain during pacing tachycardia. Table 1 summarizes the patients' profiles, including coronary anatomy, baseline left ventricular pressures, left ventricular end-diastolic volume indexes, and ejection fraction of the beats under three conditions (i.e., baseline, postpacing, and postpacing after administration of nifedipine) and total duration of pacing in each patient. All six control patients tolerated 10 full minutes of pacing.

**Effects of pacing-induced ischemia on hemodynamics and ventricular function**

*Patients with CAD (figure 1, A).* In the postpacing beats, the heart rate did not change significantly (control, 68 ± 13 beats/min vs postpacing, 63 ± 15 beats/min), nor did the left ventricular peak systolic pressure (control, 150 ± 18 mm Hg vs postpacing, 160 ± 35 mm Hg). The left ventricular peak systolic pressure increased in eight patients and decreased in three. There was a substantial increase in the left ventricular end-diastolic pressure (control, 13 ± 4 mm Hg vs postpacing, 26 ± 4 mm Hg, p < .01). The ejection fraction decreased significantly in postpacing beats (control, 62.1 ± 6.7% vs postpacing, 51.6 ± 10.6%, p < .01), as did the percent shortening of the ischemic segment (control, 34.4 ± 14.3% vs postpacing, 16.7 ± 13.1%, p < .01), but the percent shortening of the control segment did not change (control, 40.8 ± 13.6% vs postpacing, 41.4 ± 17.5%). The relaxation time constant, measured in seven patients in whom a micromanometer-tipped catheter was used, increased significantly in postpacing beats (control, 44 ± 9 msec vs postpacing, 59 ± 7 msec, p < .01), implying impairment of myocardial relaxation with ischemic intervention.

The peak rate of left ventricular filling and the LVPV/EDV tended to increase with ischemic intervention, but not to a statistically significant degree. The LVPV/EDV did not change after ischemic intervention (control LVPV, 289 ± 119 ml/sec vs postpacing, 319 ± 139 ml/sec; control LVPV/EDV, 4.71 ± 3.01/sec vs postpacing, 5.99 ± 3.81/sec; control LVPV/EDV, 3.09 ± 2.00/sec vs postpacing, 2.98 ± 1.64/sec).

**FIGURE 1.** A, Effects of pacing-induced ischemia on hemodynamics and ventricular function. Control data are shown by open bars and postpacing data by shaded bars. The heart rate (HR) and the peak left ventricular pressure (LVP) did not change significantly. The left ventricular end-diastolic pressure (LVEDP) rose significantly with ischemic intervention. Impairment of ventricular ejection is indicated by decreases in the ejection fraction (EF) and the percent shortening (%L) of the ischemic segment. The relaxation time constant (Time Constant) increased significantly, implying impairment of relaxation with ischemia. The %L of the control segment did not change in postpacing beats. The peak rate of early left ventricular filling (LVPF), the LVPF/EDV, and the LVPF/SV did not change significantly.

B, Effects of pacing-induced ischemia on regional myocardial dynamics. Control data are shown by open bars and postpacing data by shaded bars. In the ischemic segment, the peak rate of lengthening (PL) decreased with pacing-induced ischemia, as did the PL/EDL. However, the PL/dL did not change with ischemic intervention. Analysis of the control segment showed a tendency to increase in these three variables in postpacing beats, but the changes did not reach statistical significance.
Thus, pacing-induced ischemia resulted in impairment of left ventricular ejection and relaxation, but it did not appreciably alter global left ventricular filling.

Control patients. The changes in the above-mentioned variables in postpacing beats in the control patients are summarized in table 2. The left ventricular end-diastolic pressure rose slightly and statistically significantly in postpacing beats, but unlike the situation in the patients with CAD, the other variables did not change significantly. The baseline left ventricular peak filling rate in the control patients was higher than that in the patients with CAD (control patients, 485 ± 151 vs patients with CAD, 289 ± 119 ml/sec, p < .01), however, the LVPF/SV and the LVPF/EDV were not significantly different.

Effects of pacing-induced ischemia on regional myocardial lengthening

Patients with CAD (figure 1). When regional wall motion was analyzed in the ischemic segment, the peak rate of lengthening decreased in postpacing beats (control, 59 ± 26 mm/sec vs postpacing, 32 ± 23 mm/sec, p < .01), as did the PL/EDL (control, 2.04 ± 0.90/sec vs postpacing, 1.19 ± 0.92/sec, p < .01). The PL/dL, however, did not change with ischemic intervention. The analysis of the control segment showed a tendency to increase for all these three variables of segmental lengthening in postpacing beats, but the changes were not statistically significant.

Control patients. The segmental lengthening variables of the anterior and the inferior segments in the control patients are summarized in table 3. The peak lengthening rate did not change in the postpacing beats as it did in the patients with CAD. When the baseline peak lengthening rate of the anterior segment in the control patients was compared with that of the ischemic segment in the patients with CAD (since the ischemic segments were anterior segments in 10 of the 11 patients with CAD), the peak lengthening rate was higher in the control patients; however, the two normalized lengthening variables, the PL/dL and the PL/EDL, were not significantly different.

Analyses of asynchrony induced by ischemia. The results of analyses of asynchrony in left ventricular filling induced by ischemia in the patients with CAD and the control patients are summarized in table 4. In the patients with CAD, the time from mitral valve opening to the left ventricular peak filling rate was slightly but not significantly decreased in postpacing beats. The absolute time difference between peak left ventricular filling and segmental peak lengthening was increased significantly by ischemic intervention in the ischemic segment but not in the control segment. In the control patients, however, there were no such changes in either of these variables. Therefore, the degree of asynchrony in left ventricular filling increased with ischemia in the patients with CAD.

Modification by nifedipine of ischemia-induced changes in hemodynamics and ventricular function. The adminis-

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**TABLE 2**

Changes in study variables in the control patients (n = 6)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>LVP</th>
<th>LVEDP</th>
<th>T (n = 5)</th>
<th>LVPF</th>
<th>LVPF/SV</th>
<th>LVPF/EDV</th>
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<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>72 ± 12</td>
<td>135 ± 38</td>
<td>9 ± 3</td>
<td>40 ± 9</td>
<td>485 ± 151</td>
<td>5.44 ± 1.25</td>
<td>3.91 ± 0.81</td>
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<tr>
<td>Postpacing</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>74 ± 7</td>
<td>119 ± 39</td>
<td>12 ± 5</td>
<td>39 ± 7</td>
<td>510 ± 249</td>
<td>5.44 ± 2.31</td>
<td>4.17 ± 1.92</td>
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<tr>
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HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVPF = peak rate of left ventricular filling; T = relaxation time constant.

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**TABLE 3**

Variables of segmental lengthening in control patients (n = 6)

<table>
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<tr>
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<th>Anterior segment</th>
<th>Inferior segment</th>
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<td></td>
<td>%dL</td>
<td>PL</td>
<td>PL/dL</td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Mean ± SD</td>
<td>54.8 ± 19.4</td>
<td>132 ± 69</td>
<td>7.77 ± 1.98</td>
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<td>Postpacing</td>
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<tr>
<td>Mean ± SD</td>
<td>54.2 ± 18.0</td>
<td>139 ± 61</td>
<td>7.86 ± 2.23</td>
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<tr>
<td>p value</td>
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%dL = shortening fraction; PL = peak rate of segmental lengthening.
TABLE 4
Analysis of asynchrony in left ventricular filling induced by ischemia

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<th>CAD group (n = 11)</th>
<th>Ischemic segment</th>
<th>Control segment</th>
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<tr>
<td></td>
<td>MVO-PF</td>
<td>ΔT</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>70 ± 47</td>
<td>31 ± 28</td>
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<tr>
<td>Postpacing</td>
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<td>21 ± 16</td>
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<td>Mean ± SD</td>
<td>41 ± 27</td>
<td>75 ± 48</td>
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Control group (n = 6)

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<th>Anterior segment</th>
<th>Inferior segment</th>
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<td>ΔT</td>
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<tr>
<td>Baseline</td>
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<td>Mean ± SD</td>
<td>64 ± 40</td>
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<tr>
<td>Postpacing</td>
<td></td>
<td>28 ± 25</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>69 ± 38</td>
<td>21 ± 18</td>
</tr>
</tbody>
</table>

Values are msec.

ΔT = time difference between peak rate of segmental lengthening and peak rate of left ventricular filling; MVO-PF = time from mitral valve opening to peak left ventricular filling.

* p < .05.

The administration of nifedipine in six patients with CAD resulted in the disappearance or diminution of anginal pain even with the same duration and rates of pacing. Three sequential left ventricular volume-time curves from a representative case (patient 1) are shown in figure 2. In the postpacing beat, there was marked reduction in the stroke volume, and with nifedipine, the left ventricular volume-time curve returned almost to the preischemic control level. Three sequential segment length-time curves in the ischemic segment and in the control segment of patient 1 are shown in figure 3. In the ischemic segment, the extent of systolic shortening diminished markedly with ischemic intervention, and it returned to almost normal after nifedipine. In the control segment, however, no such difference in systolic shortening was seen.

Figure 4 shows the effects of nifedipine in modifying ischemia-induced changes in hemodynamics and ventricular function of six CAD patients. The changes in hemodynamics and ventricular function induced by ischemic intervention were similar in this subgroup and in the whole group, and the systolic pressure increased significantly in postpacing beats (control, 159 ± 19 mm Hg vs postpacing, 180 ± 31 mm Hg, p < .01).

After the administration of nifedipine, the same duration and rate of pacing resulted in an increase in the heart rate (control, 73 ± 12 beats/min vs postpacing, 73 ± 12 beats/min vs nifedipine and postpacing, 86 ± 18 beats/min) and changes toward normal.

![FIGURE 2](http://circ.ahajournals.org/)

**FIGURE 2.** Three sequential left ventricular volume-time curves obtained by frame-by-frame analysis of a left cine ventriculogram from a representative patient. Solid circles represent data obtained from control left ventriculography, open circles that from postpacing left ventriculography, and triangles that from postpacing left ventriculography after nifedipine. With pacing-induced ischemia, a marked reduction in the stroke volume was seen. After administration of nifedipine, the left ventricular volume-time curve returned almost to the preischemic control curve. ** p < .01. NS = statistically not significant. n = 11.
in the left ventricular end-diastolic pressure (control, 13 ± 4 mm Hg vs pacing, 25 ± 4 mm Hg vs nifedipine and postpacing, 20 ± 5 mm Hg), the ejection fraction (control, 65.5 ± 11.1% vs pacing, 52.0 ± 12.0% vs nifedipine and postpacing, 60.5 ± 11.6%), the shortening fraction of the ischemic segment (control, 43.7 ± 7.8% vs pacing, 20.2 ± 6.3% vs nifedipine and postpacing, 33.2 ± 9.7%), and the relaxation time constant (control, 44 ± 10 msec vs postpacing 62 ± 6 msec vs nifedipine and postpacing, 49 ± 4 msec, n = 5). The peak rate of early left ventricular filling and the LVPF/SV tended to increase successively but not statistically significantly (control LVPF, 342 ± 132 ml/sec vs pacing, 361 ± 155 ml/sec vs nifedipine and postpacing, 408 ± 121 ml/sec; control LVPF/SV, 6.25 ± 3.12/sec vs postpacing, 7.47 ± 4.68/sec vs nifedipine and postpacing, 7.52 ± 3.65/sec). The LVPF/EDV did not change significantly (control, 4.07 ± 2.27/sec vs pacing, 3.67 ± 1.87/sec vs nifedipine and postpacing, 4.30 ± 1.39/sec) (figure 4).

In the ischemic segment, the reduction in the peak rate of lengthening of the postpacing beat showed a tendency toward normalization, but it did not reach statistical significance. The reduction in PL/EDL in the postpacing beat returned to the control preschismic level with the administration of nifedipine (control, 2.56 ± 0.56/sec vs pacing, 1.46 ± 0.32/sec vs nifedipine and postpacing, 2.14 ± 1.27/sec). No significant differences were found in the PL/dL.
In the control segment, the administration of nifedipine resulted in increases in the peak rate of segmental lengthening, the PL/dL, and the PL/EDL (control PL, 75 ± 20 mm/sec vs postspacing, 85 ± 19 mm/sec; control PL/EDL, 117 ± 16 mm/sec; control PL/dL, 7.02 ± 1.42/sec vs postspacing, 8.03 ± 2.84/sec vs nifedipine and postspacing, 10.14 ± 3.80/sec; control PL/EDL, 3.29 ± 0.70/sec vs postspacing, 4.63 ± 0.58/sec) (figure 4, C). Since the extent of shortening did not change significantly under the three conditions (control, 11 ± 1 mm vs postspacing, 12 ± 4 mm vs nifedipine and postspacing 12 ± 3 mm), the increase in the PL/dL after administration of nifedipine was due entirely to an increase in the peak rate of segmental lengthening.

The ischemia-induced change in the time between the peak lengthening rate in the ischemic segment and peak left ventricular filling was reduced by the administration of nifedipine (table 5). That is, the degree of asynchrony induced by ischemia was diminished by nifedipine.

**Discussion**

Effects of ischemia on left ventricular filling and regional myocardial lengthening. When the heart rate is not rapid, ventricular filling occurs in two phases, early rapid filling and late filling due to atrial contraction. The
predominant filling takes place during early rapid filling. The peak rate of early ventricular filling demonstrated by radionuclide angiography in patients with CAD has been shown to be diminished, and the abnormality of early ventricular filling has been reported to be independent of left ventricular systolic function and the presence or absence of previous myocardial infarction. However, a recent study by Carroll et al. in which left cine ventriculography during exercise was analyzed showed that early left ventricular filling was augmented during exercise in patients with ischemia as well as in patients without ischemia. They showed that the rise in peak filling rate during exercise was due to a higher filling pressure in patients who developed ischemia. Furthermore, Aroesty et al. who used radionuclide ventriculography during pacing, have also shown that the peak rate of early left ventricular filling was increased during ischemia, but the rise in peak filling rate seen during intermediate levels of pacing tachycardia in patients with ischemic heart disease was blunted or even fell at the highest pacing rates. They also concluded that the rise in filling rate was induced by the higher left atrial pressure. Thus, both of these recent studies indicate that early left ventricular filling is not impaired but rather augmented during ischemic intervention. They concluded that an increase in left atrial pressure is an important factor causing an increase in the rate of early left ventricular filling during ischemia.

The results of global analysis of early left ventricular filling in the present study agree with the findings of the two recent studies. That is, with ischemic intervention, despite impairment of ventricular ejection, impairment of relaxation, and accentuation of asynchrony in left ventricular filling, the rate of early left ventricular filling was not impaired. Normalization of the peak rate of early filling for the stroke volume and the end-diastolic volume had a similar outcome. Regional analysis in the present study showed reduction in the percent segmental shortening and the peak rate of segmental shortening in the ischemic segment with ischemia. In the ischemic segment, the PL/EDL also diminished with ischemia; however, the PL/dL did not change. Analysis of the control segment showed some increase in segmental shortening, in the peak rate of segmental shortening, the PL/dL, and the PL/EDL; however, these changes were not statistically significant.

Two important mechanisms must be considered in the interpretation of the changes in the segmental shortening rate with ischemia. The first mechanism relates to elastic recoil. Using an isolated heart muscle preparation contracting in physiologic sequence with the aid of a servo system, Tamiya et al. found that the maximum velocity of isotonic muscle shortening during diastole depends solely on the extent of muscle shortening during systole, and that the changes in preload, afterload, and inotropic state alter the isotonic shortening velocity only because these factors affect the extent of shortening, so that the maximum shortening velocity divided by the extent of muscle shortening (dL/dt max/ΔL) remains constant when these factors are altered. Therefore, the process of isotonic muscle shortening simply resembles the recoiling of a spring. Although Tamiya et al. did not test the effect of hypoxia or ischemia on isotonic muscle shortening velocity, from the results of the present study we can conclude that one mechanism of reduction in the peak rate of lengthening with ischemia in the ischemic segment is due to a decrease in the extent of shortening with ischemia, since the PL/dL did not change with ischemia.

The second mechanism is impairment of myocardial distensibility with ischemia. Although the PL/dL in the ischemic segment did not change with ischemia, this variable in the control segment tended to increase with ischemia in the CAD patients. This difference may indicate impairment of distensibility with ischemia in the ischemic segment, since an increase in the left ventricular end-diastolic pressure, that is, an increase in left atrial pressure, seems to augment the index PL/dL. Using an isolated rat heart muscle preparation contracting in physiologic sequence, we have indeed shown that the slope of the relation between the maximum rate of isotonic muscle shortening and end-systolic muscle length diminishes during hypoxia. In other words, we have shown that at a given degree of muscle shortening, the maximum rate of isotonic muscle lengthening decreases with hypoxia. Therefore, in
an experimental system where the other factors that affect the rate of isotonic muscle lengthening can be controlled, impairment of myocardial distensibility with hypoxia has been demonstrated.

The ischemic process impairs myocardial relaxation\(^6\), \(^7\), \(^22\)-\(^{26}\) and results in asynchrony of left ventricular filling.\(^7\), \(^27\) When a filling pressure or a driving pressure increases, as indicated by an elevation in left ventricular end-diastolic pressure in our study, the peak rate of left ventricular filling should increase substantially. One of the factors that contributes to a blunting of the effect of an increase in a driving pressure on the left ventricular filling rate is impairment of myocardial distensibility with ischemia, which we have discussed above. The other factors we should consider are impairment of left ventricular isovolumetric relaxation and accentuated asynchrony in left ventricular filling induced by ischemia. These two factors, which have been shown previously to affect left ventricular filling, were also observed in our patients with CAD during ischemia.\(^27\), \(^28\)

It is interesting to note that the time from mitral valve opening to the left ventricular peak filling rate was decreased in postspacing beats, although the change did not reach statistical significance (table 4). The mechanism is thought to be related to a reduction in the filling volume as reflected by a reduction in the stroke volume (stroke volume index = end-diastolic volume index \(\times\) ejection fraction/100; table 1) with the same or even slightly increased early left ventricular filling rate in the postspacing beats. The time of the peak rate of early left ventricular filling usually occurs near at the midpoint of the rapid filling phase. Therefore, the midpoint comes earlier and the time from mitral opening to peak left ventricular filling becomes shorter when the filling volume is smaller with a slightly increased filling rate.

**Effect of nifedipine.** After the administration of nifedipine, postspacing systolic function and relaxation moved toward their preischemic levels. The beneficial effects of nifedipine on left ventricular response to pacing-induced ischemia in patients with CAD have been demonstrated by Lorell et al.\(^29\) Their findings with respect to left ventricular end-diastolic pressure, ejection fraction, and other indexes in 11 of their 17 patients were similar to those in the present study. Since they found no changes in left ventricular \(+dP/dt\) after nifedipine, a negative inotropic effect was not considered to be the mechanism for the symptomatic and hemodynamic improvement due to nifedipine during ischemia. The mechanism of the beneficial effects of nifedipine in myocardial ischemia has been attributed, by Lorell et al. and others, to a decrease in oxygen demand secondary to its unloading effect,\(^30\)-\(^32\) an increase in oxygen supply due to its vasodilating effect,\(^33\)-\(^35\) and direct protection from ischemic myocardial damage.\(^36\), \(^37\) Although the difference did not reach statistical significance, the peak rate of global early left ventricular filling showed a tendency to increase with nifedipine during ischemia, and the abnormality in the peak rate of lengthening of the ischemic segment, which decreased in postspacing beats, was normalized with nifedipine.

It is interesting to note that in the control segment, the peak rate of lengthening, the PL/dL, and the PL/EDL increased with nifedipine, although the percentage of shortening in the control segment remained unchanged under the three conditions. The reason for this is not clear; however, a similar finding has been noted in other studies with other calcium-channel blockers. For instance, Murakami et al.\(^28\) have shown that the intravenous administration of 15 mg of diltiazem to patients with CAD resulted in improved isovolumetric relaxation and early diastolic left ventricular filling, despite an increase in left ventricular end-systolic volume, a decrease in ejection fraction, and unchanged left ventricular end-diastolic pressure. In their study, the peak rate of left ventricular filling increased uniformly with diltiazem, even in patients with a normal ejection fraction. An increase in the postspacing heart rate with nifedipine might affect the peak rate of segmental lengthening. However, Tamiya et al. demonstrated in isolated heart muscle that the dL/dt max/\(\Delta L\) remained constant when the contraction frequency was changed over a range of 45 to 180 contractions/min. Therefore, the increase in the PL/dL in the control segment after nifedipine cannot be attributed to the changes in heart rate. Likewise, changes in afterload and possible reflex-induced catecholamine release secondary to nifedipine administration cannot be the mechanism for improvement in the lengthening of the control segment with this drug, since these factors did not affect the dL/dt max/\(\Delta L\) ratio in the study of Tamiya et al.\(^20\)

Using the perturbation method in an isolated rat cardiac muscle preparation contracting in physiologic sequence, Zile et al.\(^38\) have recently shown that an increase in load on a muscle during isotonic lengthening, which is independent of preload and load during muscle contraction, increases the rate of isotonic muscle lengthening. The left ventricular end-diastolic pressure in the postspacing beat after the administration of nifedipine was elevated above the baseline pressure in our study. Therefore, an increase in driving pressure is probably one of the mechanisms of an increase in the
three variables of segmental lengthening in the control segment. However, the postpacing left ventricular end-diastolic pressure with nifedipine was lower than that without nifedipine, but the three variables of the postpacing beat after nifedipine in the control segment were higher than those without nifedipine. Therefore, an increase in driving pressure alone cannot explain the augmentation with nifedipine of lengthening in the control segment. Many of our patients with CAD had minor stenoses in the coronary arteries that supplied the control segment. Although the stenoses were insignificant, they might have potentiated the ischemia. Nifedipine might have improved latent ischemia in the control segment by improving coronary circulation or by improving possible calcium overload present in the myocardium of patients with CAD. The latter has been postulated to be an important mechanism in the preservation of cardiac contraction and prevention of contracture by nifedipine in experimental ischemia and improvement of relaxation and diastolic filling by nifedipine in hypertrophic cardiomyopathy. Calcium overload has been demonstrated by Lorell and Barry to cause reduction in contraction and lengthening of cultured chick embryo cells. They also have shown that a calcium-channel blocker, verapamil, corrects contraction and lengthening abnormalities during calcium overload.

**Limitations of the study.** We used monoplane right anterior oblique cineangiography for frame-by-frame analysis of left ventriculograms. In some patients, an abnormality in segmental contraction and lengthening can be detected only in the left anterior oblique projection because the septal and posterolateral left ventricular walls are not visualized in the right anterior oblique projection. However, according to Cohn et al., these two zones in the left anterior oblique projection are not asynergic in the absence of corresponding involvement of the anterior, apical, or inferior zones in the right anterior oblique projection, and the prevalence of asynergy is not altered by the addition of the left anterior oblique view. A close correlation has also been reported between left ventricular volume calculated from the biplane and monoplane projections. In our study, in which most of the patients had significant stenoses in the left anterior descending coronary artery, the right anterior oblique projections showed contraction and lengthening abnormalities in the anterior left ventricular segment in the postpacing beats. Therefore, we do not think that the use of biplane left ventricular cineangiography altered the outcome of the study substantially.

The left ventricular peak filling rate tended to increase while the peak lengthening rate of the ischemic segment decreased significantly and that of the control segment increased only slightly without statistical significance (figure 1). We do not think that this dissociation resulted from the fact that we did not use biplane left ventricular cineangiography since the ventricular volume and the segmental length were calculated from the data obtained from the same right anterior oblique projection ventriculogram. The control and the ischemic segments were of representative radii chosen by the criteria described in Methods. To extrapolate the segmental data to the whole left ventricular volume, one has to consider the plane distribution of each segment. For instance, even if the control segment showed only a small increase in the peak rate of segmental lengthening and the ischemic segment showed a significant reduction in the rate, but the plane distribution of the control segment were wider than that of the ischemic segment, the peak rate of left ventricular filling could increase. Another factor that we should take into consideration is accentuated asynchrony in left ventricular filling. As shown in the table 4, the time difference between peak left ventricular filling and segmental peak lengthening was increased in the ischemic segment but not in the control segment in the postpacing beats. This factor could also cause dissociation.

Although we studied postpacing hemodynamics and left ventricular dynamics in the control patients without significant coronary artery lesions and compared the results with those in the patients with CAD, we did not study the effect of nifedipine in the control patients. Since all of the control patients had chest pain that required cardiac catheterization and coronary angiography, we performed an ergonovine provocation test if the coronary arteriogram, left ventriculogram, and postpacing left ventriculogram were all normal, and we could not administer nifedipine before the ergonovine provocation test. Even if the ergonovine provocation test was negative, it was impossible to perform the third left ventriculogram after nifedipine and pacing because of the time required and the possible effect of ergonovine on hemodynamics and left ventricular dynamics. Therefore, the mechanism of the increase in the rate of segmental lengthening, the PL/dL, and the PL/EDL in the control segment in postpacing beats after nifedipine is still unclear. Although this was not proven, we believe nifedipine improved latent ischemia and have discussed other possible mechanisms. Further experimental or, if possible, clinical studies are needed to elucidate this mechanism.

In conclusion, acute ischemia causes reduction in the segmental myocardial lengthening rate due to a de-
crease in segmental shortening and impairment of myocardial distensibility. Despite impairment of isovolumetric relaxation, accentuation of asynchrony in left ventricular filling, and a decrease in the peak rate of segmental lengthening in the ischemic segment, the peak rate of global left ventricular filling does not decrease with ischemia due to an increase in the peak rate of lengthening in the nonischemic segment secondary to an increase in left ventricular filling pressure. Administration of nifedipine results in improvement in segmental lengthening in ischemic as well as in control segments in the postpacing beat. Nifedipine may improve myocardial lengthening in patients with CAD even in apparently nonischemic segments.

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Effects of pacing-induced ischemia on early left ventricular filling and regional myocardial dynamics and their modification by nifedipine.

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